THE EFFECTS OF CHRONIC EXERCISE ON THE HEART AND ON CORONARY ATHEROSCLEROTIC HEART DISEASE. A LITERATURE SURVEY

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A Literature Survey

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This technical report has been reviewed and is approved for publication.

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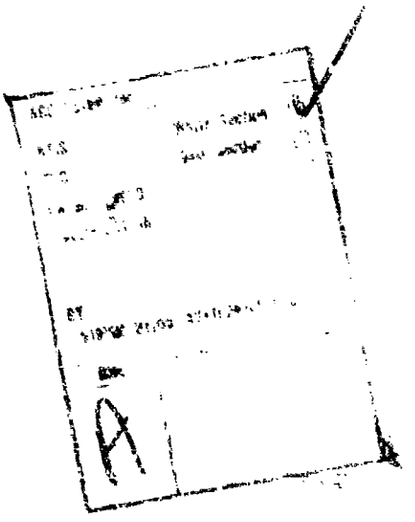

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Detailed information is presented here concerning a comprehensive literature survey on epidemiologic, pathologic, and animal studies evaluating the effects of chronic exercise on the heart and on coronary artery disease. No definitive conclusion could yet be reached. Alteration of the three cardinal risk factors--cholesterol, hypertension and cigarette smoking--should be the main aim of preventive cardiology efforts.

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C O N T E N T S

T A B L E S

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INTRODUCTION

Although aerobic exercise training has well-defined effects on the heart (1) and on cardiovascular function (2), its effects on atherosclerosis (1) and coronary heart disease morbidity and mortality remain uncertain (3, 4). Physical inactivity has not been demonstrated to act as a risk factor for coronary heart disease to the same level of confidence as the three cardinal risk factors--hypercholesterolemia, hypertension, cigarette smoking (5). Nonetheless, many individuals are exercising on a regular basis for cardiovascular fitness under the assumption that this will protect them from the manifestations of coronary heart disease. In fact, many professionals in the health fields are recommending fitness programs for the prevention of coronary heart disease and for rehabilitation after myocardial infarction. For numerous reasons, including both the danger of death due to coronary heart disease during exercise (6-10) and the importance of giving the proper priority to National health efforts for fighting the coronary heart disease epidemic, it is important to clarify the relationship of aerobic exercise training to coronary heart disease. In Table 1 are listed those areas of scientific study that are reviewed, in this report, to clarify this relationship:

TABLE 1. AREAS REVIEWED FOR PERTINENT STUDIES OF THE EFFECTS OF PHYSICAL ACTIVITY ON CORONARY ATHEROSCLEROTIC HEART DISEASE

1.	Population or clinical studies evaluating the effect of physical activity on coronary atherosclerotic heart disease
2.	Animal studies of the effect of chronic exercise on atherosclerosis and the heart
3.	Studies evaluating the effects of exercise on factors that could affect the progression of myocardial ischemia

POPULATION OR CLINICAL STUDIES

The major pertinent population or clinical studies, as listed in Table 2, are the subject of the opening section of this report. The first three types of these studies are defined as follows: "Retrospective"

TABLE 2. POPULATION OR CLINICAL STUDIES, EVALUATING THE RELATIONSHIP OF PHYSICAL ACTIVITY TO CORONARY HEART DISEASE, LISTED BY THE YEAR(S) IN WHICH THEY WERE REPORTED

A. RETROSPECTIVE EPIDEMIOLOGIC STUDIES
1. ENGLAND AND WALES MORTALITY STATISTICS, 1953 (11, 12)
2. LONDON BUSMEN, 1953 (12)
3. MALMO, 1958 (16)
4. NORTH DAKOTA, 1959 (17)
5. CHICAGO MORTALITY STATISTICS, 1960 (18)
6. CALIFORNIA MORTALITY STATISTICS, 1960 (19)
7. CANADIAN VA, 1961 (20)
8. U.S. RAILMEN, 1962 (21)
9. U.S. POSTMEN, 1963 (22)
10. SOUTH AFRICAN RAILROAD, 1963 (23)
11. HEALTH INSURANCE PLAN OF NEW YORK, 1966 (24)
12. ISRAEL KIBBUTZIM, 1966 (25, 26)

B. PREVALENCE OR CROSS-SECTIONAL EPIDEMIOLOGIC STUDIES
1. PEOPLE'S GAS COMPANY, 1960 (27)
2. U.S. RAILROAD, 1962 (21)
3. EVANS COUNTY, GEORGIA, 1965 (28)

C. PROSPECTIVE EPIDEMIOLOGIC STUDIES
1. LOS ANGELES CIVIL SERVANTS, 1964 (29)
2. LONDON BUSMEN, 1966 (14)
3. CHICAGO ELECTRIC COMPANY, 1969 (30)
4. U.S. RAILROAD, 1970 (21)
5. PEOPLE'S GAS COMPANY, CHICAGO, 1970 (31)
6. SEVEN COUNTRY STUDY, 1970 (32)
7. SAN FRANCISCO LONGSHOREMEN, 1970 and 1975 (33,34)
8. WESTERN COLLABORATIVE GROUP, 1970 and 1975 (35,36)
9. GOTESBURG, SWEDEN, 1971 and 1975 (37, 38)
10. FRAMINGHAM, MASSACHUSETTS, 1971 (39, 40)
11. EVANS COUNTY, GEORGIA, 1971 (41)
12. LONDON CIVIL SERVICE, 1973 (42)
13. NATIONAL CORONARY DRUG STUDY, 1975 (43)

D. PATHOLOGICAL STUDIES
1. ENGLAND, 1958 (44)
2. WESTCHESTER, 1960 (45)
3. CLARENCE DeMAR--AUTOPSY, 1961 (46)
4. OXFORD, 1967 (47)
5. JAFFA, 1970 (48)
6. BASSLER, 1973 (49)
7. FINLAND, 1975 (50)

E. REHABILITATION STUDIES
1. TEL AVIV, 1968 (52)
2. CLEVELAND, 1969 (51)
3. RECHNITZER ET AL., 1972 (53)
4. NATIONAL COLLABORATIVE POSTINFARCTION STUDY
5. REDWOOD ET AL., 1972 (58)
6. ROUSSEAU ET AL., 1973 (55)
7. KATTUS ET AL., 1972 (59)
8. KAVANAGH AND SHEPHARD, 1974 (62)
9. FLETCHER AND CANTWELL, 1974 (63)
10. FERGUSON ET AL., 1975 (64)

studies are epidemiologic studies involving populations in whom data were obtained in the past, not specifically for epidemiologic purposes. "Prevalence" studies are epidemiologic studies which screen a population for the current manifestations of a disease. "Prospective" studies are epidemiologic studies involving a cohort of individuals specifically chosen and studied for the purpose of following them over a subsequent period of time for the development of disease.

Retrospective Epidemiologic Studies

In one of his many epidemiologic studies evaluating physical inactivity as a risk factor for coronary heart disease, Morris presented the data from the occupational-mortality records for England and Wales (11, 12). Physical activity was graded by occupation. The level of activity was based on an independant evaluation of the occupations by several industrial experts. The activity level of the last job was found to be inversely related to the mortality from coronary disease, as determined from death certificates. In another study, Morris screened records for the incidence of coronary heart disease in drivers and conductors of the London Transport System. The age-adjusted total incidence of coronary disease was 1.5 times higher, and the sudden and three-month mortality was 2 times higher, in the driver group than in the conductor group. The difference in physical activity was only deduced by knowing that one group drove the buses while the other group conducted on the double-deck vehicles. In 1956, however, Morris published a paper subtitled "The Epidemiology of Uniforms," which reported that the drivers had greater girth than the conductors (13). A later study in 1966 by Morris also showed that the drivers had higher serum cholesterol and higher blood pressures than the conductors (14). Moreover, a study by Oliver documented that, for some unknown reason, even the recruits for the two jobs differed by lipid levels and weight (15).

Forssman and Lindegard organized a study in Malmo, a Swedish town of about 200,000 people (16). The study group was comprised of all male survivors of an acute myocardial infarction, admitted to their hospital from 1948 to 1955; and their age at the onset of the study was 55 years or less. This group included 66 men for whom healthy, similar age controls were randomly selected from the town. The level of activity was determined by an analysis of their occupation. No differences in occupational physical activity were found between the controls and the postinfarction group.

Zukel et al., who analyzed data from a population of 106,000 individuals living in six counties in North Dakota (17), reported that farmers had slightly less total coronary heart disease and one-half the infarctions and deaths from coronary disease than the others. Zukel et al. did not relate this finding directly to differences in physical activity, because they were aware of socioeconomic and environmental differences between the two groups (17). However, they did administer a physical activity questionnaire to survivors of myocardial infarctions and to matched controls. Zukel et al. felt that the results from their questionnaire suggested that physical activity could be protective from the manifestations of coronary disease.

Stamler et al. analyzed the mortality statistics from Chicago for 1951 and 1953 (18). The authors found no significant occupational group differences in age specific coronary heart-disease death rates for white males, ages 45 to 64 years.

Breslow and Buell analyzed census and death certificate data in California from 1949 to 1951 (19). They felt that the data revealed a gradient of decreasing mortality from coronary heart disease with increasing physical activity, but only when occupational groups of similar general mortality were considered.

Shapoff and Little studied a group of men with documented myocardial infarction randomly selected from the files of the Toronto Veterans Administration Hospital and matched to a group from the hospital files of patients admitted with non-chronic illnesses (20). The individuals were questioned as to lifelong activity, with assessment of their physical activity in childhood, youth, and adult life. The conclusion of the author was that coronary heart disease was not associated with habitual physical inactivity.

Taylor et al. have reported on the mortality of white males employed by the U.S. railroad industry (21). The employees were separated by job title into three groups representing three levels of physical activity. Death certificates for the years 1955 and 1956 were analyzed by these groupings and age-adjusted death rates were obtained. Taylor et al. concluded that the data were consistent with the hypothesis that men in sedentary occupations suffer a higher incidence of coronary heart disease mortality than those in occupations requiring moderate to heavy physical activity (21).

Kahn gathered information from Federal employee records to analyze mortality data on men who were appointed to positions in the Washington, D.C., post office from 1906 to 1940 (22). The study was designed to test the physical activity hypothesis by comparing the mortality data of sedentary clerks to active mail carriers. Kahn adjusted for the effect of the transfer from active jobs to inactive jobs by considering a sub-sample of men who did not change jobs. The data from this preselected group suggested that the clerks had 1.4 to 1.9 times the mortality from coronary heart disease than the carriers.

Adelstein compared white South Africans working for the South African railroads as officers (sedentary) to those working as employees (active) (23). Mortality secondary to coronary heart disease during 1954 to 1959 among these employees, when age-adjusted, did not differ from the general population. No significant differences were found in mortality from coronary disease for the two levels of occupational physical activity.

Frank and colleagues studied 301 men enrolled in the Health Insurance Plan of Greater New York (HIP) who had their initial myocardial infarction in 1961-1963 (24). On-the-job and off-the-job activities were assessed by a questionnaire. This assessment was made during a personal interview with

those who survived their myocardial infarcti.. and with the wives of those who had died. The authors concluded that this assessment of physical activity on and off the job permitted identification of a group of least active men who were much more likely to experience a clinically severe episode and die within four weeks of its onset than men who were relatively more active.

Brunner surveyed Jews of European origin living in the Kibbutzim, or collective settlements, in Israel from 1946 to 1961 (25, 26). Sedentary workers, defined as those who spent 80% or more of their time at work sitting, had 2.5 to 4 times the incidence of coronary heart disease as all the other workers. Brunner believes that this population was ideal for study because their mode of life eliminated socioeconomic differences.

Prevalence or Cross-sectional Studies

In 1958, a complete evaluation was made of male employees of a utility company in Chicago (27). [illegible] of coronary heart disease was determined by reviewing in[illegible] records for diagnostic electrocardiographic changes or for [illegible] patible with coronary disease. The prevalence of coronary disea[illegible]wer in the blue-collar workers than in the white-collar workers, and also lower in the non-sedentary than in the sedentary men. There was little difference in major risk factors between the activity levels.

From 1957 to 1959, a sample of 3,049 U.S. railroad men were randomly selected for the purpose of studying the prevalence of risk factors for coronary heart disease (21). Active switchmen and sedentary clerks and executives composed the two different activity groups compared. The results suggested that the switchmen had less coronary disease. However, Taylor has pointed out that the results were compounded by many factors (21). Of particular note was the fact that the switchmen with coronary disease often become clerks. He concluded that the majority of factors affecting the observed prevalence of coronary disease operated to exaggerate any true protective influence of physical activity.

In 1960, the population of Evans County, Georgia, was first studied for the prevalence of coronary heart disease (28). Disease endpoints were angina, a history of a myocardial infarction, or diagnostic electrocardiographic findings. Among white males, in this biracial study, the distribution of coronary disease by occupation suggested that those with a greater activity had less coronary heart disease. Black males were found to have less coronary disease than white males and were more active, both by analysis of occupation and caloric consumption; but they were also thinner and had lower serum cholesterols.

Prospective Epidemiologic Studies

Chapman and Massey randomly selected 1,403 healthy white males, employed as civil servants in Los Angeles in 1949, with a mean age of 47 (29). After

an initial examination, periodic followup examinations and yearly questionnaires were completed. At the time of the 11-year followup, no difference in the incidence of coronary heart disease was observed according to socioeconomic class or the level of physical activity as determined by job title.

Morris and colleagues evaluated 687 healthy London busmen (14). Five years later, the busmen were re-examined and there were 47 cases of coronary disease diagnosed, including sudden death, myocardial infarction, electrocardiographic changes, and angina. Incidence rates per 100 men for the five years were 4.7 for conductors and 8.5 for drivers. However, the drivers were found to have significantly higher blood pressures and serum cholesterols than the conductors.

Paul followed 1,719 white males, age 40 to 55, randomly selected from the employees of the Hawthorne Electrical Works in Chicago (30). After eight years of followup, there were 24 deaths due to coronary disease, 53 acute myocardial infarctions with survival, and 80 patients with angina. Activity off the job was assessed by a personal interview. Approximate differences in caloric expenditure and intensity of work were determined for shop and office workers and also with special means for two different classes of shop workers. No difference was found in coronary disease among the different levels of activity.

Taylor studied the effects of occupational activity differences among railroad men (21). Energy expenditure was estimated by activity and dietary analysis. After five years of followup, no difference was found in coronary disease incident rates between the active and the sedentary groups.

Stamler and colleagues evaluated 1,241 apparently healthy male employees of the People's Gas Company in Chicago (31). After seven years of followup, coronary disease mortality was higher in blue-collar workers with an estimated greater activity at work than in white-collar workers. Stamler felt that this finding was consistent with the hypothesis that groups of men with similar findings with respect to the "cardinal risk factors" (hypertension, hypercholesterolemia, and cigarette smoking) would experience similar mortality rates for coronary disease, irrespective of the habitual physical activity of work.

The Seven Countries Coronary Artery Disease Study consists of collaborate groups in Japan, Yugoslavia, the United States, Finland, Italy, Netherlands, and Greece (32). The methodology of this excellent study has been described in detail elsewhere, and is a model for epidemiologic investigation. Data from the first five years of followup showed no difference in coronary disease incidence between physically active and sedentary men. The ten-year analysis, soon to be reported, will be of much interest.

Paffenbarger (an accomplished long-distance runner) and his colleagues have reported two separate studies of San Francisco longshoremen. The first study involved 3,263 males who were followed for 16 years (33). Two classes of workers, differing by about 925 calories in workday expenditure,

were identified. As defined, the less active group had a 33% higher coronary death rate. In the second study, 6,351 men were followed for 22 years, or to death, or to the age of 75 (34). Their longshoring experience was computed in terms of work-years according to categories of high, medium, and low caloric output. The effect of job transfers was accounted for by reclassifying the men annually according to their work assignments. The age-adjusted coronary death rate for the high activity category was 26.9 per 10,000 work-years, and the medium and low categories had rates of 46.3 and 49.0. This protective "threshold" effect was seen especially for sudden death. It was concluded that repeated bursts of high energy exercise established a plateau of protection against coronary mortality.

The Western Collaborative Group Study was initiated in 1961 with emphasis on psychologic patterns. Annual followup studies were obtained on over 3,000 healthy men who initially were 35 to 59 years old. New coronary events, including symptomatic myocardial infarction, angina, and electrocardiographic changes were recorded. The customary exercise habits of each participant were obtained by personal interview. After 4.5 years of followup, the annual incidence of coronary disease was 10 per 1,000 for men without regular exercise habits, compared to 7.4 per 1,000 in men with exercise habits (35). This difference was due to symptomatic myocardial infarction; for no difference was observed in the incidence of silent infarction, angina, or in recurring infarction. Fatal myocardial infarction had occurred in 2 per 1,000 men without regular exercise habits compared to 0.5 per 1,000 with exercise habits. The data were reanalyzed after 8.5 years of followup (36). No significant difference in the coronary disease incident rate was found when considering physical activity at work or other exercise habits, except in the group 50-59 at the time of entry. In that group, those who had regular exercise habits had approximately one-third less coronary disease than those with no regular exercise habits.

In 1963, Werko began a study of a cohort of one-third of all men born in 1913 in the industrial Swedish town of Goteaburg. This cohort consisted of approximately 800 men, all 50 years of age, and without signs or symptoms of coronary disease. In the first report after 4 years of followup, there were 23 acute myocardial infarctions (37). The 23 men who had symptomatic infarction were questioned in order to assess, retrospectively, their activity level on and off the job one year prior to their infarction. Activity levels were categorized as light, moderate, or heavy. A random sample of healthy men in the cohort were questioned in a similar fashion, and by comparison, the sample men were more active. After 10 years of followup, Tibblin et al. presented a second report on this cohort (38). By that time, 19 men had died of coronary disease and 31 had survived an acute myocardial infarction. Physical activity during work was classified as sedentary, moderate, or heavy, according to the type of occupation held at 50 years of age. No significant difference in physical activity was found between those who developed coronary disease and those who did not. When using leisure time activities, there was a trend towards inactivity in those who were later to develop coronary disease.

In the Framingham study, the level of physical activity was assessed using a 24-hour history of usual physical activity, and a physical activity index arrived at from five classifications of activity status (39, 40). A number of physiologic measurements hypothesized to be parameters of physical activity were determined for each participant, including resting heart rate, vital capacity, hand grip strength and relative weight. Coronary heart disease and mortality were subsequently found to be higher in the cohorts with indices or measurements consistent with a sedentary life style.

Cassel and colleagues have reported a seven-year followup of the individuals found to be free of coronary disease in Evans County after their prevalence study (41). Among non-farming occupations, occupational physical activity no longer showed a protective effect against the development of coronary disease. However, the lower prevalence rate in white farmers compared to white non-farmers, and Blacks compared to Whites, was confirmed in this prospective study. One explanation for these findings was that only a sustained level of physical activity as performed in farming was protective against coronary disease. This explanation was supported by a trend discovered between leisure time and on-the-job physical activity and the prevalence of coronary disease.

Morris and colleagues studied British males who were government office workers (42). They utilized a questionnaire which evaluated leisure time physical activity. After a two-year followup, 232 men had suffered their first clinical attack of coronary disease. Each of these men was matched by age with two colleagues not so affected. From the questionnaire, the activities of the men were analyzed and those who reached leisure time activity peaks of approximately 7.5 kcal/min were classified as vigorous. Eleven percent of the men who developed coronary disease and 26% of the controls were considered vigorous. Those recording vigorous exercise were at about one-third the relative risk of developing coronary disease as those who did not.

The Coronary Drug Project was a nationwide collaborative study to evaluate, in double-blind fashion, the efficacy of certain drugs to prevent the manifestations of coronary disease in men who had already had a myocardial infarction (43). Many parameters were assessed prior to the study, including leisure time physical activity. In the placebo group, the five-year percentage of death was 14.4% for the moderate or vigorous men as compared to 23.8% for the sedentary men.

Pathologic Studies

Morris and Crawford sent out requests to several hundred British pathologists to complete a standard questionnaire on autopsies of men 45 to 70 years old (44). The last occupation was estimated (by its title) as involving light, active, or heavy physical activity. The results of 3,800 autopsies on individuals dying of causes other than coronary disease were gathered from 1954 to 1956. Ischemic myocardial fibrosis and complete coronary occlusion were commoner in lighter occupations, but coronary atheromata and narrowing were of equally high prevalence in all occupation groups.

The results of 207 consecutive autopsies of white males, age 30 to 60, who died from accidents, homicide or suicide, were reported by Spain and Bradess (45). The autopsies were done in the medical examiner's office of Westchester County, New York. The men were considered as active or sedentary (by occupational title) with approximately 100 in each group. No significant differences were found in the degree of atherosclerosis between those engaged in sedentary and those engaged in physically active occupations.

Currens and White presented the autopsy results of Clarence DeMar, a famous long-distance runner, who died of rectal carcinoma (46). He was still running long distances until shortly before his death at age 70. His coronary arteries were found to be two to three times normal size with some atherosclerotic involvement, but it did not encroach on the luminal area.

Measurements were made from radiographs of injected coronary arteries in two autopsy studies at Radcliff Infirmary, Oxford (47). Ninety-two cases without postmortem evidence of myocardial infarction were used as controls; and 79 cases were used who had evidence of acute or healed infarction. The right coronary artery measured in a nondiseased segment was assumed to reflect the diameter of the coronary arteries. The physical activity of the last occupation was determined (from the job title) as light, active, or heavy. The diameter of the right coronary artery in normals increased with age, but the infarction cases showed a smaller diameter of the right coronary artery in each age group. The data were only suggestive that, in normals, the right coronary artery diameter increased with the activity of work--while in the infarction group, it decreased. These differences were not statistically significant and no determination of the degree of atherosclerosis was made.

A group of pathologists in Jaffa, Israel, reported the results of consecutive autopsies on 172 European-born Jews who were victims of traumatic deaths (48). According to personal documents and some information obtained from relatives, 93 had led a sedentary life and 79 were manual workers. Each coronary artery was cross-sectioned at 1.0-cm intervals to measure internal and external diameters. The percentage of narrowing of the vessels was calculated using these measurements. There was no significant difference between the active and inactive groups.

Recently, T. J. Bassler has published letters stating that his personal experience, as a pathologist and as an active participant in the American Medical Joggers Association, has led him to the conclusion that "immunity to a heart attack coexists with the ability to cover 42 kilometers on foot." Though his letters are referenced with publications bearing his name from reputable scientific journals, these all turn out to be "letters-to-the-editor." Thus, his statements are totally conjecture and not based on any scientific study. I have had the experience of knowing of men with exceptional physical fitness who have had severe coronary artery disease, and have reported one such case (49). Opie has reported a number of long distance runners who have died of coronary atherosclerotic heart disease (8).

Proponents of the physical activity hypothesis have always been upset by the high incidence of coronary disease in the very active eastern Finlanders. A recent pathologic study has shown how unknown factors can confuse epidemiologists in trying to demonstrate the influence of one factor in the etiology of this multi-factorial disease. Pesonen and colleagues (50) have reported an autopsy study of infants who died in Finland. The left coronary arteries were thicker in the eastern group, and supported the hypothesis that the thickenings were a genetic component in the etiology of coronary disease. If the physical activity hypothesis is true, this finding could explain the high incidence of coronary disease in the east Finlanders in spite of their vigorous physical activity.

Rehabilitation Studies

Hellerstein has reported his seven-year experience in a prospective study of the effects of physical fitness on the course of coronary heart disease (51). His program also modified other risk factors by advising an antiatherogenic diet, the avoidance of cigarettes, and weight loss. Over the followup period, his patients experienced a death rate of 2 per 100 subject-years. In a group of conventionally treated patients, the death rate was 5 per 100 subject-years. Unfortunately, this study was not double-blind, and there was selection of the healthier patient group by the exclusion of those patients who could not tolerate an exercise program. Also, other risk factors were modified.

Gottheiner has presented data on over 1,000 men with coronary heart disease who remained in his rehabilitation program in Israel for five years (52). Initially, the group consisted of 1,500; but nearly one-third dropped out. His program involved careful advancement through gradually more intensive exercise, with testing prior to advancement to a higher stage. It culminated in competitive team games for those who progressed to the upper fitness categories. The author suggested that the use of competitive sports maintains the participant's interest in the program. He reported a mortality rate of 3.5% over five years of followup, compared to 12% in a comparable series of physically inactive postinfarction patients in Israel. Similar to other rehabilitation studies, there was a selection of a healthier patient group by the loss of those unable to tolerate the exercise program.

Rechnitzer and his colleagues in Canada have reported their five- and seven-year followup of survival and recurrence rates after myocardial infarction in exercising and control subjects (53). The seven-year study consisted of 68 men under age 51, with a previous myocardial infarction, who participated in a program of graduated exercises for seven years. The controls fulfilled the criteria to enter the exercise program, but did not. The exercising subjects experienced a 3% recurrence rate and a 7.6% death rate, as compared with a 12% recurrence rate and a 15% death rate in the controls. A second comparison of recurrence and survival over a five-year period was made between 77 patients, who had remained in an exercise program for a minimum of three months, and 127 control subjects. The exercising subjects manifested a 1.3% recurrence rate and

a 3.9% death rate, while the controls had a 28% recurrence rate and 11% death rate. Although the results of their investigations suggested that an exercise program in a selected group may favorably affect prognosis following recovery from myocardial infarction, the results should be interpreted cautiously. One or more variables (such as blood pressure, angina, and serum cholesterol), not related to the exercise program, may have been operative in producing the apparent benefits. Recently, in the United States, a national collaborative postinfarction study has begun. It is performed in a double-blind fashion; the major risk factors are controlled, and only the activity status of the postinfarction subjects will be directly altered. Hopefully, this study will clarify the relationship of exercise training and prognosis after a myocardial infarction.

The hemodynamic changes secondary to physical conditioning have been the subject of many studies and I have reviewed these studies in detail previously (2). They are summarized in Tables 3 and 4. In short, at submaximal levels of exercise, maximal oxygen consumption increases and heart rates decrease. The latter beneficially allows a longer time during diastole for myocardial perfusion. However, it has been debated whether the increase in maximal oxygen consumption is due to an increased cardiac output or to a widening of the AVO_2 difference (54). Recently, Rousseau and colleagues have demonstrated in trained cardiac patients that the higher maximal oxygen consumption was due almost exclusively to a greater maximal AVO_2 difference (55). This finding supports the concept that, in cardiac patients, the improvement in performance with physical conditioning is due to increased peripheral extraction of oxygen by the working muscles. However, some cardiac patients probably also have an improvement in cardiac function (56, 57).

Redwood and his colleagues studied the hemodynamic effects of a six-week intensive training program in seven patients with angina (58). Training resulted in a marked increase in exercise capacity. A hemodynamic index of myocardial oxygen consumption (triple product) was less at any level of exercise after training and a higher index value could be achieved prior to angina. They concluded that physical training improved exercise performance by reducing the heart rate and blood pressure response to exercise, and their findings also suggested that myocardial oxygen delivery was enhanced.

Kattus and his colleagues reported 30 asymptomatic men who had abnormal responses to exercise testing (59). Thirteen of them participated in a supervised physical training program that led to an increased exercise capacity. Four of these men normalized their electrocardiographic response to treadmill testing; but, of the 17, who did not train, two normalized their exercise electrocardiogram. The significance of these findings is uncertain, since it has been well documented that an abnormal exercise test is only 20%-30% predictive of coronary artery disease in asymptomatic men (60, 61).

Kavanagh and colleagues in Canada have reported eight postinfarction patients from their rehabilitation center who were able to compete in the Boston Marathon (62). While these patients ran, they were accompanied by their physicians--with resuscitation equipment--in automobiles. These investigators did not advocate marathon running as a casual pastime for postmyocardial infarction patients. However, their patients did show that a remarkable level of function is possible through training, even in post-infarction patients.

Fletcher and Cantwell have reported their outpatient exercise program for patients with recent myocardial infarctions (63). They reported 42 patients who participated in three months or more of a gym program of walking and jogging, calisthenics and volleyball. There was a significant increase in treadmill exercise capacity--and a decrease in resting and peak exercise systolic blood pressure and resting heart rate, body weight, and serum triglycerides. Of three patients with abnormal ST segment depression on initial submaximal treadmill tests, two had a normal test after the exercise program. This study suggests that a medically supervised gym exercise program for patients with recent myocardial infarctions is feasible, safe, and beneficial.

Ferguson and his colleagues in Canada entered 14 patients, with angiographically documented coronary artery disease, in a 13-month physical training program (64). After training, there was a 25% increase in maximal oxygen consumption. Coronary angiography was repeated; and new collateral vessels, observed in only two instances, appeared to have developed in response to a progression of coronary artery disease. The increased exercise capacity after training in these patients was not due to the development of the coronary collateral circulation as evaluated by coronary angiography.

ANIMAL STUDIES

In the evaluation of the physical activity hypothesis, limited human studies are available on the morphologic and metabolic changes in the cardiovascular system due to exercise training. This limitation is due to the difficulties controlling interfering variables, the reluctance to perform serial invasive procedures, the lack of cardiac tissue for analysis, the inability to make accurate measurements of the size of the coronary arteries and the ventricular wall and cavity, and time as well as expense. For these reasons, a careful review of the pertinent animal studies on the effects of chronic exercise is of importance in understanding some of the ways exercise can influence the cardiovascular system (1). In Table 5 are listed the areas reviewed in this section.

TABLE 3. STUDIES OF THE HEMODYNAMIC EFFECTS OF PHYSICAL CONDITIONING (ref. 2)

STUDY	NO. OF MEN	AGE	DAYS BETWEEN STUDIES	TYPE OF TRAINING
DALLAS (119)	3 sedentary men and 2 athletes	18-21	55	Interval and continuous; 6 days a week for 1½ hours a day
STOCKHOLM (120)	8 sedentary men	19-27	120	Continuous; 3 days a week for 1 hour a day
VERMONT (121)	9 athletes	18-24	90	Dash and continuous; daily for 1-2 hours
HELSINKI (122)	14 sedentary men	19-26	60	Hard basic military training
STOCKHOLM-GOTHENBURG (123)	15 sedentary men	38-55	63	Interval and continuous; 2-3 days/week for 1 hr/day
VERMONT (124)	7 sedentary men	40-49	200	Competitive paddle ball for 1 hour, 3 times a week
GOTHENBURG (125)	5 sedentary men with CAD (coronary artery disease)	44-55	180	Bicycle ergometer 3 times a week
HELSINKI (126)	6 sedentary men with CAD	37-55	50	Bicycle ergometer 3 times a week
SEATTLE-LOUVAIN (127)	12 sedentary men with CAD	34-68	90	Submaximal aerobic exercise 3 times a week
COPENHAGEN (128)	7 sedentary men with CAD	46-60	30-70	Bicycle ergometer 5 times a week

TABLE 4. HEMODYNAMIC CHANGES SECONDARY TO PHYSICAL CONDITIONING AS DEMONSTRATED BY THE REPORTED STUDIES (ref. 2)

STUDY	REST							SUBMAXIMAL EXERCISE										MAXIMAL EXERCISE								
	HR	SBP	DBP	CO	SV	O_2C	AVO_2D	TYPE OF EXERCISE	HR	SBP	DBP	CO	SV	O_2C	ME	LA	AVO_2D	INTENSITY OF EXERCISE	HR	SBP	DBP	CO	SV	MO_2	LA	AVO_2D	TYPE OF EXERCISE
Dallas (young normals)	↓	–	–	–	↓	↑	↑	Supine & treadmill	↓	–	–	–	↑	–	–		–	Multiple levels	–	–	–	↑	↑	↑	–	↑	Supine & treadmill
Stockholm (young normals)	↓	–	–	↓	–	↑	?	Sitting (bicycle ergometer) (BE)	↓	–	–	–	↑	↑	↑	↓	↑	Multiple levels	↓	↑	↑	↑	↑	↑	?	↑	Sitting (BE)
Vermont (young athletes)	↓	–	–	↓	↓	↓	X	Treadmill	↓	–	–	↓	↓	↑	↓		X	Low									
									↓	–	–	–	–	↓	↑		X	High									
Helsinki (young normals)	↓	–	–	↑	↑		X	Supine	↓	↓	↓	–	↑				X	Moderate									
Stockholm-Gothenburg (older normals)	↓	(mean) ↓		–	–	–	X	Sitting (BE)	↓	(mean) ↓		–	↑	–	–	↓	–	Multiple levels	↓	(mean) –	–	↑	↑	↑	↑	–	Sitting (BE)
Vermont (older normal)	↓	–	↓	–	–	↓	X	Treadmill	↓	↑	↓	↓	↑	↓	↑		X	Low	↓	X	X	X	X	↑	X	X	Sitting (BE) without catheters
									↓	↑	↑	↓	–	↑	↓		X	High									
Gothenburg (coronary artery disease) (CAD)	↓	(mean) ↓		↓	–	–	–	Sitting (BE)	↓	(mean) ↓		↓	–	–	–	↓	↑	5 & 25 min during exercise									
Helsinki (CAD)	–	–	–	–	–	–	–	Supine	↓	–	–	↓	↑	↓	↑	↓	–	Low									
									↓	–	↓	↑	↑	–	–	↓	–	High									
Seattle-Louvain (CAD)	↓	(mean) ↓		↓	–	–	↑	Sitting (BE)	↓	(mean) ↓		↓	–	–			↑	Multiple levels	↑	X	X	X	X	↑	X	X	Bicycle or treadmill without catheters
Copenhagen (CAD)	↓	↓	↓	↓	↑	–	X	Sitting (BE)	↓	↓	↓	↓	↓	–	–	↓	X	Low									
									↓	↓	↓	↓	↑	–	–	↓	X	High									

NOTE: For key to signs, acronyms, and symbols--consult facing page.

--- KEY TO TABLE 4 ---

Signs

– no change	X not performed
↑ increase	↟ slight increase
↓ decrease	↡ slight decrease

Acronyms and Symbols

AVO_2D	=	arteriovenous oxygen difference	HR	=	heart rate
BE	=	bicycle ergometer	LA	=	lactic acid concentration
CAD	=	coronary artery disease	ME	=	mechanical efficiency
CO	=	cardiac output	MO_2	=	maximal oxygen consumption
DBP	=	diastolic blood pressure	O_2C	=	oxygen consumption
SBP	=	systolic blood pressure			

TABLE 5. THE TOPICS OF ANIMAL STUDIES CONCERNING THE EFFECTS OF CHRONIC EXERCISE ON THE CARDIOVASCULAR SYSTEM (AS REVIEWED IN THIS REPORT)

1. Myocardial hypertrophy
2. Myocardial histologic changes
3. Coronary artery size changes
4. Coronary collateral circulation
5. Cardiac performance
6. Myocardial mitochondria enzymes and glycogen stores
7. Atherosclerosis and serum cholesterol

Myocardial Hypertrophy

Numerous studies have demonstrated that vigorous exercise can produce cardiac hypertrophy in the animals (65-70). This hypertrophy rapidly regresses when the exercise training is discontinued (65). It is generally believed that exercise-induced hypertrophy serves as a useful adaptive mechanism to improve myocardial contractility and increase cardiac work capacity. Poupa and his colleagues have reported that the heart/body ratios are invariably larger in the wild than in the domestic form of an animal species (66). Leon, Bloor, and associates (67, 68) have presented data showing that the heart hypertrophies with exercise in young rats--whereas, in old rats, exercise causes a decline in heart weight due to a loss of myocardial fibers. Tomanek and his coworkers (69) have also demonstrated age-dependent myocardial hypertrophy in exercised rats.

Myocardial Histologic Changes

Poupa, in comparing domesticated to wild animals, found that the density of muscle cells and capillaries was much greater in the more active wild animals (66). In an experiment utilizing surgical constriction of the aorta, Poupa induced a 35% increase in heart weight in one-month-old and in adult rabbits (66). In the young rabbits, the hypertrophied hearts showed a normal capillary density; but, in the adult rabbits, it was decreased. He hypothesized that in young animals, cardiac hypertrophy was secondary to fiber hyperplasia, while in older animals, it was secondary to cellular hypertrophy. Also, he hypothesized that the capillary bed responds most markedly to exercise performed at an early age.

Tomanek studied the age-related response of the ventricular capillary bed and myocardial fiber width in male rats to chronic exercise (70). After a period of chronic exercise, the rats were euthanized. The myocardial fiber width was unchanged while the capillary/fiber ratio increased in the exercised rats as compared to the control rats in all age groups. The capillary density decreased with age, and was increased over the controls only in the young exercised rats. Leon and Bloor (68) have also demonstrated that, although the response of the rat heart to chronic exercise varied with age, the capillary to fiber ratio increased at all ages.

Coronary Artery Size Changes

Tepperman and Pearlman studied the effects of exercise on the coronary tree of rats by the corrosion-cast technique (71). After an exercise program, the animals were euthanized, their hearts were weighed, and then their coronary arteries were injected with vinyl acetate. The hearts were digested with potassium hydroxide and the casts of the coronary arteries were weighed alone. Compared to the controls, the exercise groups had an increased heart to body weight ratio and an increased coronary tree cast weight to heart weight ratio.

Stevenson and coworkers used the same corrosion-cast technique to ascertain the effects of exercise of different types, frequency, and duration (72). They found that, in the rat, forced exercise caused an increase in the coronary tree size as compared to the cardiac weight, provided the exercise was not too strenuous or frequent. Leon and Bloor (68) demonstrated that swimming exercise in rats caused an increased luminal cross-sectional area of the main coronary arteries in the animals that developed an increase in ventricular weight; that is, only in the youngest of the strenuously exercised rats. These results are supported by the studies of Karr and colleagues that demonstrated coronary artery enlargement in rats with cardiac hypertrophy induced by hypoxia, aortic constriction, and thyroxin (73). Also, it has been shown in autopsy studies that the relationship between total heart weight and the diameter of the coronary arteries is linear in man up to the upper weight limit of physiologic hypertrophy (74).

Coronary Collateral Circulation

Eckstein studied the effects of exercise and artificial coronary artery narrowing on coronary collateral flow (75). He surgically induced a constriction in the circumflex artery of approximately 100 anesthetized dogs. Various degrees of narrowing were induced, but only dogs that developed electrocardiographic changes were included in the study. After one week of rest, the dogs were divided into two groups. One group was exercised on the treadmill regularly for two months, and the other group remained at rest in cages. Then, the animals were anesthetized, a second thoracotomy was performed, and their blood pressure was stabilized mechanically. The circumflex artery was isolated and divided beyond the surgical constriction. Flow rate through the constriction and the flow rate from the distal end of the artery were measured. The flow rate through the constriction was considered to be inversely related to the degree of constriction. When these values were plotted against one another, it was shown that the less the antegrade flow or the greater the constriction, the greater the retrograde or collateral flow. Also, the exercised dogs had a greater value for retrograde flow than the rested dogs with any degree of constriction. These results demonstrated that moderate and severe arterial narrowing resulted in collateral flow proportional to the degree of narrowing, and that exercise led to even greater collateral flow.

Burt and Jackson used similar methods to study the effects of exercise on the coronary collateral flow of normal dogs (76). Prior constriction of a coronary artery was not performed as in Eckstein's experiments. After one month of treadmill exercise, surgery was performed and retrograde flow was measured from the distal portion of the circumflex artery with its proximal end ligated. No difference was found in retrograde flow between the control and the exercise groups.

Kaplinsky and coworkers studied the effects of five weeks of treadmill exercise on dogs after complete occlusion of the left anterior descending coronary artery (77). The exercised dogs and a control group were euthanized, and selective cineangiography and postmortem coronary injections demonstrated extensive collateral formation; but no difference was found between the two groups.

Cobb and associates studied the effects of exercise on acute coronary occlusion in dogs who already had an artificial partial occlusion (78). The anterior descending coronary artery was partially occluded in 50 dogs, and then the dogs were divided into a control and an exercise group. After a training period, a complete occlusion of the anterior descending artery was surgically produced. The dogs were monitored for arrhythmias for six days, then euthanized, and their hearts removed. The coronary vessels were injected and the collateral vessels quantitated radiographically. The two groups did not differ as to the extent of the infarct relative to the partial occlusion, the frequency of arrhythmias, or the extent of radiographically quantitated collaterals.

Cardiac Performance

Penpargkul and Scheuer have reported the effects of physical training on the mechanical and metabolic performance of the isolated rat heart (79). Exercised rats and controls were euthanized and their hearts isolated in a perfusion apparatus with cannulas inserted for life support, pressure and flow measurement, and metabolic analysis. When compared with sedentary controls, the hearts from conditioned rats had higher levels of cardiac work and output. Atrial pacing at increased rates caused greater differences in these parameters, and left ventricular pressures and DP/DT became higher in the conditioned hearts. Atrial pacing also resulted in greater oxygen consumption in conditioned hearts, whereas higher lactate and pyruvate concentrations occurred in sedentary hearts. Raising atrial filling pressures resulted in ventricular function curves which were superior in the conditioned hearts. Also, there were greater increments in oxygen consumption, a higher aerobic/anaerobic energy production ratio, and increased coronary artery flow. In the physically trained rats, the function of the heart as a pump was improved, and this was at least partially due to improved oxygen delivery. Scheuer has excellently reviewed the subject of physical training and intrinsic cardiac adaptations (80).

Crews and Aldinger have studied exercise hypertrophied rat hearts (81). After an exercise program, a thoracotomy was performed and isometric

systolic tension was measured while the animals were physiologically supported. This measurement is felt by the authors to reflect potential contractility and cardiac work. Measurements were also made of left ventricular pressure before and during aortic constriction. The findings supported the concept that the exercise hypertrophied heart was functionally superior to the normal heart. Aldinger has reported a similar study involving a control and an exercise group of rats receiving Digitoxin (82). The study demonstrated that, unlike the pathologic hypertrophy of disease, exercise hypertrophy and the increment in myocardial function concomitant to the hypertrophy were not altered by Digitoxin.

Myocardial Mitochondria Enzymes and Glycogen Stores

Arcos and his colleagues (83), who studied female rats, used a protocol similar to that used by Aldinger. The rats were separated into a control group and into three swimming groups, with total swimming time ranging from 60 to 500 hours. The rats were euthanized and their hearts analyzed. Mitochondrial mass was increased only in the rats that swam for approximately 160 hours. Electron-microscopy showed increased size and number of mitochrondria in this group, while mitochondrial degeneration was noted in rats exercised for a longer time. No change in the respiratory rate of mitochondrial homogenates was found between the groups. The microscopic and histochemical sections showed evidence of myocardial degeneration in the exercised rats.

Aldinger and Sohal repeated the previous experiment with the total swimming time increased to between 400 and 1500 hours (84). Also, a control and an exercise group treated with Digitoxin were included. Again, mitochondrial degenerative changes were seen in the myocardium of the non-treated swimmers; however, the swimmers receiving Digitoxin showed no degenerative changes. In fact, they had an increase in the size of mitochondria and the number of mitochondrial cristae. The swimmers had an increased mitochondrial to myofibril ratio, occasional areas of myocardial hemorrhage, increased distance between nuclei, and dilatation and vesicle formation within intercalated discs.

Banister et al. have reported a study of the effects of chronic exercise on myocardial mitochondria morphology using electron-microscopy (85). Male rats were run on a treadmill for one hour a day over a 65-day period. Throughout the training period, four animals were euthanized on certain days: one control; one trained animal, euthanized immediately after exercise; one euthanized 30 minutes after exercise; and one euthanized 24 hours after exercise. On the first training day, exhaustive running resulted in myocardial degeneration in animals euthanized immediately and 30 minutes after exercise. The rat euthanized 24 hours after exercise showed myocardial morphology similar to that of the control rat. The effect of training began to appear after ten days. Fewer altered mitochondria were seen in trained rats euthanized at any period after exercise. This demonstrated that with physical training, exhaustive exercise has a less damaging effect on myocardial mitochondria, suggesting that this organelle adapts to exercise.

Oscai and colleagues (86, 87) have studied rats by using various exercise protocols, including the same swimming protocol used by Arcos and Aldinger. They could not confirm an increase in mitochondrial protein or respiratory enzymes in the mitochondria of exercised rats. They found that the capacity for aerobic metabolism of untrained rat myocardium was adequate to meet the increased demands for ATP imposed by an exercise program without increasing mitochondrial mass or respiratory capacity. Respiratory enzyme levels were approximately five times higher in the heart than in the gastrocnemius muscle.

Scheuer and coworkers have measured increased cardiac glycogen stores in conditioned rat hearts, but found no increase in the concentration of high energy phosphate compounds (88). However, physical training in rats resulted in an increase in adenosine triphosphate activities of cardiac actomyosin, crude myosin, and purified myosin (89-91). These contractile protein enzymatic activities probably relate to potential myocardial contractility. The increase in adenosine triphosphate activity was found to be related to the intensity and the duration of the training program. Further studies indicated that training may induce a chemical change at the locus of enzymatic activity on myosin at its site for interaction with actin (91). These findings regarding the contractile proteins probably explain the increased contractility in the hearts of conditioned animals.

Atherosclerosis and Serum Cholesterol

McAllister and colleagues have reported an experiment demonstrating an accelerated effect of treadmill exercise on experimental atherosclerosis (92). Ten dogs were placed on identical high cholesterol diets of equal caloric value and 150 mg of thiouracil daily. The diet and thyroid antagonists were used to shorten the time period of the study. The dogs were treated identically except that five were trained to run five miles a day. At the end of one year, angiograms were performed; then the dogs were euthanized, and their arteries analyzed for the extent of atherosclerosis. During the course of the study, the serum cholesterols progressively rose, with the runners having higher values. The runners also showed more atherosclerosis than the sedentary dogs in all vessels, including the coronaries.

Myasnikov and his colleagues reported the results of a study performed in Russia (93). Ten rabbits were given a high cholesterol diet; 25 rabbits received the same diet but were exhausted daily on a treadmill; and 8 rabbits received no cholesterol but were exercised. The exercised rabbits on a high cholesterol diet had lower serum cholesterols than those not exercised. At the end of six months, the animals were euthanized; and visual estimation suggested that the exercise reduced the development of atherosclerosis in the aorta and coronary arteries. For unknown reasons, however, there were more marked pathologic changes in the myocardium of the exercised rabbits receiving cholesterol than in either of the other groups. Kobernick and his coworkers reported the results of a similar study (94). Eighteen rabbits were fed a high cholesterol diet and exercised for ten minutes a day, while a non-exercised matched group received

the same diet. Serum cholesterol values did not differ between the groups. After 13 weeks the rabbits were euthanized, and their aortas inspected visually for atherosclerosis and chemically analyzed for cholesterol. Exercised rabbits had greater muscle mass, less body fat, and less aortic atherosclerotic involvement than the non-exercised rabbits.

Warnock and his colleagues reported an exercise study using young male roosters (95). All of the birds were fed an atherogenic diet. Approximately half were exercised while the others remained caged. Weekly serum cholesterol values were determined and found to be lower in the exercised birds. The food consumption was supposedly equal in both groups but the exercised birds were heavier. At the end of 14 weeks, the birds were euthanized and the aorta, its main branches, and samples of brain and liver were assayed for cholesterol. The cholesterol content was lower in the assayed vessels and liver of the exercised birds than in the non-exercised birds. Weiss performed a similar study on adult chickens (96). No significant difference was found in the degree of atherosclerosis in the thoracic and abdominal aorta of chickens maintained at three different activity levels.

Carlson has reported the results of strenuous exercise on the serum cholesterol of old rats (97). The trained group ran three hours daily for one month. At the end of this period, the serum cholesterol averaged 186 mg% in the trained group and 250 mg% in the control group. The extent of atherosclerotic involvement was not studied. Carlson found that lipid levels in rats increased with age as they do in man. Faris et al. performed a similar study using young rats (98). Both control and exercised animals had serum cholesterol readings of about 45 mg%, and there were no statistical differences between the groups. Hebert and Lopez also studied the effects of exercise on serum lipids in rats of unstated age (99). After 10 weeks, the rats who exercised voluntarily in a revolving drum had less of a weight gain, larger adrenal glands, lower serum cholesterol, lower serum triglycerides, and lower liver G-6-PD levels than did the sedentary controls.

FACTORS ACTING INDIRECTLY THROUGH PHYSICAL ACTIVITY

There are factors affected by exercise that could alter myocardial ischemia or atherosclerosis. Some of these are listed in Table 6 and are briefly reviewed in this section.

TABLE 6. FACTORS [illegible] EXERCISE TRAINING COULD INFLUENCE, AND THAT COULD AFFECT MYOCARDIAL ISCHEMIA AND/OR ATHEROSCLEROSIS

1. Blood coagulation and fibrinolysis
2. Serum cholesterol
3. Serum triglycerides
4. Blood pressure
5. Susceptibility to fatal arrhythmias
6. Neuro-humoral factors
7. Excess weight

The possibility has long been postulated that an increase in fibrinolytic action secondary to exercise could prevent coronary thrombosis, but recent studies have not confirmed this theory (100, 101). However, the investigation of platelet adhesiveness may yield pertinent findings (102). The studies of the effects of exercise on serum cholesterol in man have been reviewed in detail by Gustafson (103). It appears that regular vigorous exercise can lower cholesterol levels somewhat; but diet, certain medical disorders, and genetic mechanisms are much more influential. Most studies, however, have shown a decrease in serum triglycerides with exercise training (104, 105). The effects of exercise training in patients with borderline or mild hypertension have been studied (106, 107). These studies have demonstrated a favorable response. Raab was a strong proponent of the theory that exercise favorably alters neuro-humoral factors influencing myocardial ischemia and that exercise could protect the heart from fatal arrhythmias (108). However, there has been little or no scientific work done to substantiate these theories. Many investigators have recommended exercise training as a method to control obesity. Carter and Phillips nicely demonstrated the structural changes that can occur secondary to exercise in middle-aged men (109). Over a two-year period, their exercise group made significant decreases in body weight, percent body fat, skin fold thickness, girth, and endomorphy as well as having a significant increase in their specific gravity.

DISCUSSION

The available data evaluating the relationship of physical activity and/or aerobic exercise training to coronary atherosclerotic heart disease and myocardial ischemia are reviewed in this section. In spite of the work of many excellent investigators, no definite conclusion can be made because the results of the available studies are both contradictory and inconclusive. The following discussion will try to explain why a definitive answer is not possible.

Many of the epidemiologic studies have dealt with occupational differences in retrospective studies. Although retrospective studies are attractive because the data are already available, such an approach has many difficulties. The information collected usually was not standardized or complete; this is especially true for physical activity which is difficult to measure. Furthermore, the population base was highly selected due to job transfers, retirement, or death. Confounding variables (such as lipids, blood pressure, and other pertinent measurements) usually were not available. These studies can have impressive numbers of man-years observed, but the biases were not eliminated by the great number of observations. With limited access to the subjects studied and with reliance on poorly standardized information, the assessment of physical activity and the diagnosis of coronary heart disease have been imprecise.

Prospective studies are better for accurately determining relative risk and minimizing the likelihood of bias, but prospective studies are comparatively expensive and difficult. Although the data collection and

methodology can be precise, classifying physical activity usually is still imprecise. Few studies have employed adequate methodology to characterize the physically active individual in accurate terms.

When the occupation or job title alone is used to assess the level of physical activity, those with latent coronary heart disease may be selected in less active work--because the sick usually transfer to less demanding jobs. Men select their jobs for personal reasons; and those with illness, symptoms, or obesity usually are more likely to obtain sedentary work. In this mechanized era, however, there is a limited gradient in on-the-job activities. Also, individuals that differ by occupation usually differ by socioeconomic status and by other risk factors. Inaccuracies of physical activity assessment often become apparent when a job assumed to be of a certain activity level is investigated closely, or when off-the-job activities are considered. Thus, job titles without an actual assessment of energy expenditure or consideration of off-the-job activity make difficult the accurate classification of individuals as active or inactive.

Assessing the level of physical activity by a questionnaire completed by the subject can be grossly inaccurate and often poorly reproducible (17). Exaggeration or denial mechanisms cause problems, particularly in post-infarction patients; and there are the usual inconsistencies due to limitations of understanding and memory. When questionnaires are administered to a population at risk (which includes individuals with angina, early symptoms of coronary disease or high risk diseases, such as hypertension and diabetes), a bias is introduced which tends to increase associations between physical inactivity and coronary heart disease. These high-risk individuals are also likely to be less active. Data from such questionnaires would relate physical inactivity to coronary disease when, in fact, physical inactivity was actually related to the high-risk condition.

The Framingham study used heart rate, obesity, vital capacity, and hand-grip strength as measurements of the level of physical activity (40). However, these measurements are indirect and dependent upon other factors. Other investigators have used caloric consumption, assuming a steady weight to assess the level of physical activity. This method depends upon food questionnaires or dietary samplings, both of which have well-known limitations and methodologic problems.

A major problem with assessing physical activity and its relationship to myocardial ischemia is that, if it truly does exert a protective influence, the specific physiologic mechanism has not been demonstrated. Certain types or patterns of exercise may be more important to assess than those already considered.

Endpoints used in population studies have included: angina, coronary insufficiency, acute myocardial infarction, diagnostic electrocardiographic changes, sudden death, and other manifestations assumed to be due to coronary heart disease. The definitions and tests for these endpoints often were not standardized, and investigators relied upon the diagnosis

of many different physicians. The problems with diagnosis by death certificate are easily appreciated. Other difficulties arise in the selection of the underlying cause of death as contrasted with immediate cause and contributing factors.

The pathologic studies were not definitive, because physical activity was estimated from the title of the last job and because differences in technique were used in determining the degree of atherosclerosis and the caliber of the coronary arteries. It is striking, though, that the three studies (44, 45, 47) investigating the degree of coronary atherosclerosis in a cohort found little or no difference between their active and sedentary groups.

With respect to the rehabilitation studies, investigators have shown that, under proper supervision, exercise training can be carried out with reasonable safety in selected patients with coronary heart disease and that the hemodynamic changes of the trained state can be achieved (2, 51-64). Importantly, the ability of these persons to tolerate physical stress can be increased and a high proportion of them are able to return to a more active life. Unfortunately, the rehabilitative studies have not been controlled and have depended upon volunteers. Also, the patients were further selected by the loss of higher risk patients physically unable to undertake an exercise program. Hopefully, the National Collaborative Postinfarction Rehabilitation Study will not have these limitations.

The animal studies have added considerable data to our knowledge of the effects of chronic exercise on the heart. They demonstrate that there are morphologic and metabolic changes that can make the cardiovascular system better able to withstand any stress, possibly even that imposed by atherosclerosis and myocardial ischemia. These favorable adaptations are more marked in younger animals than in older animals. However, the data regarding a beneficial effect of chronic exercise on the atherosclerotic process or on serum cholesterol levels are in no way definitive. In general, the animal studies support the therapeutic and preventive use of exercise. They suggest, however, that efforts to motivate individuals to exercise should be adjunctive to the modification of the cardinal risk factors--hypercholesterolemia, cigarette smoking, and hypertension (5, 110).

Since there are inadequate data at this point to demonstrate that regular physical exercise stops the atherosclerotic process or protects the heart from the progression of myocardial ischemia, reasons against its recommendation must be considered. In spite of many excellent reviews of physical activity and coronary heart disease (111-114), little attention has been given to the negative aspects. Blackburn's balanced approach to this matter should be noted (115, 116).

The danger of exercise in persons with coronary heart disease, even in those with asymptomatic disease, has been demonstrated (6-10). Surprisingly, most myocardial infarctions do not occur during exertion (117, 118), but

this may be due to physiologic warnings that make persons with coronary heart disease limit their activities. The advice to "get more exercise" may be enough to make a person ignore these warnings and exceed the limits of his myocardial blood supply. Besides the mortality associated with exercise, there can be significant morbidity, especially in older individuals. Infarctions have been reported, and even carefully supervised training programs have a significant incidence of orthopedic problems. Another consideration is the expense of facilities, equipment, and supervision for exercise.

SUMMARY

The data regarding the effect of physical conditioning on the progression of myocardial ischemia, although suggestive of a favorable influence, are in no way definitive. Efforts to alter the physical activity habits of our population should not supersede efforts to alter the major risk factors. The emphasis in the prevention of coronary atherosclerotic heart disease for the general public should be on the well-established cardinal risk factors, that is, hypercholesterolemia, hypertension, and cigarette smoking. The National Collaborative Postinfarction Rehabilitation Study, when completed, may demonstrate how physical conditioning influences the progression of myocardial ischemia. However, "moderate activity is a part of a balanced satisfying living and is the safe and sane hygienic prescription of the thoughtful physician for his patients, the high risk and the healthy alike" (116).

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